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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/664,958	09/22/2003	Kyoko Koibuchi	241461US0CONT	6750

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OBLON, SPIVAK, MCCLELLAND, MAIER & NEUSTADT, P.C.
1940 DUKE STREET
ALEXANDRIA, VA 22314

EXAMINER	
MOORE, WILLIAM W	

ART UNIT	PAPER NUMBER
1656	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/664,958	KOIBUCHI ET AL.	
	Examiner	Art Unit	
	William W. Moore	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 August 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *20030922, 20031024*, & 20040816.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

SDO

DETAILED ACTION

Priority

Applicant's claims in the Declaration of Inventorship filed 18 July 2003, and at the first page of the specification as amended on 2 July 2004, to priority under U.S.C. § 365(c) of the 15 March 2002 filing date of the International patent application PCT/JP02/02476, of which the instant application is a continuation, and to foreign priority of the Japanese patent applications JP 2001-078930 and JP 2001-293348 filed, respectively, 19 March and 26 September 2001, are hereby acknowledged.

Information Disclosure Statement

Applicant's three Information Disclosure Statements [IDS] filed on 22 September and 24 October 2003, and on 16 August 2004, are hereby acknowledged. A duplicate citation of Lee et al., 1998, has been lined-through to avoid redundant citation on the face of a patent issuing on the instant application.

Preliminary Amendment

Applicant's Preliminary Amendment to the specification filed 2 July 2004 has been entered, providing the history of the instant application. Claims 1-9 pending in the application were the subject of a Requirement for Restriction mailed 28 July 2005 to which Applicant timely replied in the Response filed 29 August 2005.

Election

Applicant's election **with** traverse filed 29 August 2005 of the invention of Group II comprising claims 1-8 drawn in part to, and claim 9 drawn entirely to, an aminopeptidase having the amino acid sequence set forth in SEQ ID NO:5, and to nucleic acid sequences encoding the aminopeptidase, is acknowledged. The traversal is on the grounds that the restriction was improperly made under a lack of unity standard rather than under the domestic restriction practice of 35 U.S.C. § 121.

Withdrawal of the restriction of record in favor of application of restriction practice of 35 U.S.C. § 121 would, however, be a disadvantage to Applicant as it would result in a four-Group restriction, dividing claims drawn to the different aminopeptidases into two Groups and dividing drawn to the differently classified nucleic acids encoding the two aminopeptidases, and associated vector and host cells claims, into another two Groups. Thus the lack-of-unity basis for restriction is maintained.

Applicant also traverses the restriction asserting that examining all claims would not entail a "serious burden". This is not found persuasive because significant differences in the amino acid sequences of the different polypeptides require separate searches in the patent and non-patent literature as explained at the close of page 2 of the Requirement for Restriction mailed 28 July 2005. The requirement as to restriction between the structurally different polypeptides, and their encoding polynucleotides, of Groups I and II is still deemed proper and is therefore made FINAL. Claims 1-9 are examined herein to the extent that they describe an aminopeptidase having the amino acid sequence of SEQ ID NO:5 and an encoding polynucleotide and claims 1-8 are withdrawn from consideration to the extent that they are drawn to another amino acid sequence.

Objection to the Specification

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code at page 13. Applicant is required to delete all embedded hyperlinks or other forms of browser-executable code. See MPEP § 608.01.

Claim Objections

Claims 3 and 6-9 are objected to because of the following informalities: Claim 3 lacks number agreement between the subject and verb in its preamble, which should be amended to recite "[A] nucleic acid molecule according to claim 2". Claims 6-8 lack a

term indicating the nature of the entity that is transformed: a cell. Clause 7 of claim 9 uses non-standard terminology in stating "non-denatured" and "denatured", as the gel is neither, and the infinitive – "denaturing" – is the term commonly used in English to refer to the conditions in which electrophoresis occurs. This aspect of the objection may be overcome by amending clause 7 of the claim to adopt the language used at page 4, lines 3-5, of the specification which better describes the aminopeptidase characteristics in appropriate, art-recognized, terms. Appropriate correction is required.

Claim Rejections - 35 USC § 101

35 U.S.C. § 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-9 are rejected under 35 U.S.C. § 101 because the claimed invention is directed to non-statutory subject matter.

None of the independent claims 1, 2, or 9 describe a "new . . . composition of matter" as required by the statute because each fails to distinguish a aminopeptidase that is present in Nature in its native state, or a nucleic acid molecule that is present in Nature in its native state from a aminopeptidase, or a nucleic acid molecule, that is a discovery, an invention reduced to practice by the efforts of a person. Claims 3-5 are included in this rejection because, like claim 2 from which they depend, they cannot distinguish a nucleic acid molecule present in Nature, where recombination events occur in chromosomes, from an invention reduced to practice by the efforts of a person. Claims 6-8 are included in this rejection because they also fail to describe an "isolated . . . host cell" and because the term "transformed" cannot distinguish the hosts of claims 6-8 from microorganisms infected by a natural process with the non-isolated DNA of claim 2, which constitutes a "transformation". This rejection as it applies to claims 1-5 and 9 may be overcome by amending claims 1, 2 and 9 to introduce an appropriate

distinguishing term that describes statutory subject matter, e.g., by reciting "[a]n **isolated** aminopeptidase" and "[a]n **isolated** nucleic acid molecule". In the absence of the presentation of any host cell claim that specifically describes a vector comprising a nucleic acid of claim 2, where claim 2 has been amended as indicated above, as the transforming agent, this rejection as it applies to claims 6-8 may be overcome by amending claim 6 to recite "[a]n **isolated** transformed . . . host **cell**".

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3 and 5-9 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The specification fails to exemplify or describe the preparation of the divergent aminopeptidases of clause (D) of claim 1 pertaining to the elected invention, divergent nucleic acid sequence of nucleic acid molecules of clause (D) of claim 2 pertaining to the elected invention encoding divergent aminopeptidases, and the nucleic acid molecules of clause (d) of claim 3 pertaining to the elected invention encoding divergent aminopeptidases where any condition of hybridization can be characterized as "stringent" relative to some other condition, thus cannot differ in scope from clause (D) of claim 2. This rejection includes claims 5-8 because they depend from claim 2 and incorporate its subject matter unsupported by the specification's disclosure and also includes claim 9 because it states no specific structural features of an aminopeptidase, thus is construed to be drawn to an altered aminopeptidase according to the definitional statement spanning pages 7-8 of the specification. Such generic aminopeptidases, and

generic DNA sequences encoding them, differ at an unknown number of positions in the amino acid sequence of SEQ ID NO:5 by alterations such as amino acid substitutions, insertions, and deletions, but neither the claims nor the specification describe where the differences occur, nor what the differences might be, that both alter the amino acid sequence of SEQ ID NO:5 yet provide a product retaining aminopeptidase activity.

The specification does not otherwise disclose or suggest the nature or source of any of the generic aminopeptidases that meet the limitations of the claims. "While one does not need to have carried out one's invention before filing a patent application, one does need to be able to describe that invention with particularity" to satisfy the description requirement of the first paragraph of 35 U.S.C. § 112. *Fiers v. Revel v. Sugano*, 25 USPQ2d 1601, 1605 (Fed. Cir. 1993). The specification furnishes no relevant identifying characteristics of aminopeptidases diverging at an unknown number of amino acid positions from SEQ ID NO:5, nor characteristics permitting a correlation between structures of undisclosed generic aminopeptidases and the structure of SEQ ID NO:5. Nothing demonstrates that, at the time the specification was filed, Applicant was "able to envision" enough of the structure of a claimed but undisclosed generic aminopeptidase, or a nucleic acid sequence encoding it, to provide the public with identifying "characteristics [that] sufficiently distinguish it . . . from other materials". *Fiers*, 25 USPQ2d at 1604 (citing *Amgen, Inc. v. Chugai Pharmaceutical Co.*, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991).

Claims 1-3 and 5-9 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for the preparation of a leucine- and methionine-specific aminopeptidase having the amino acid sequence set forth in SEQ ID NO:5, as well as the preparation of nucleic acid sequences encoding the aminopeptidase, does not reasonably provide enablement for the preparation of aminopeptidases having amino acid sequences that diverge from SEQ ID NO:5 by an unknown number of amino acid sequence alterations of unknown character, or for the preparation of nucleic acid molecules encoding such divergent aminopeptidases. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 1-3 and 5-9, construed according to the definitional statement that spans pages 7-8 of the specification, contemplate an unknown number of arbitrary amino acid substitutions, additions or deletions in the aminopeptidase amino acid sequence of SEQ ID NO:5, where an aminopeptidase of claim 9 may be such a divergent aminopeptidase and the preparation of nucleic acid molecules encoding the divergent aminopeptidases. This rejection is not, however, directed to the preparation of nucleic acid molecules that are isocoding with the DNA acid sequence of SEQ ID NO:4. The specification cannot support introduction of even a few amino acid sequence alterations in the amino acid sequence of SEQ ID NO:5, where the alterations are amino acid insertions, deletions, or substitutions anywhere, in any combination or any pattern, in the aminopeptidase amino acid sequence set forth in SEQ ID NO:5. Indeed, neither the prior art concerning other fungal leucine aminopeptidases made of record herewith nor Applicant's specification can identify, taken together, even a few amino acids in the amino acid sequence of SEQ ID NO:5 that might be altered, nor teach the nature of an alteration that may be made, which permits a resulting polypeptide to retain its function as a leucine aminopeptidase.

Mere sequence perturbation cannot enable the design and preparation of nucleotide sequences encoding a myriad of divergent aminopeptidases and provide the public with a nucleotide sequence encoding an enzyme that retains its native function. This is well demonstrated by the publication of Seffernick et al., 2001, **Journal of Bacteriology**, Vol. 183, No. 8, pages 2405-2410, made of record herewith, who teach that the alteration of 9 amino acids in a sequence of 475 amino acids, a scant 2% of the native amino acid positions, in a deaminase will suffice to alter its substrate specificity and require it to catalyze different reactions even though, p. 2409, these alterations do not at all alter its tertiary structure and are spread throughout its primary structure.

It is well settled that 35 U.S.C. § 112, first paragraph, requires that a disclosure be sufficiently enabling to allow one of skill in the art to practice the invention as claimed without undue experimentation and that unpredictability in an attempt to practice a claimed invention is a significant factor supporting a rejection under 35 U.S.C. §112, first paragraph, for non-enablement. See, *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (discussing eight factors relevant to analysis of enablement). Applying the factors discussed in *Wands* to Applicant's disclosure, it is apparent that:

a) the specification lacks adequate, specific, guidance for altering the leucine aminopeptidase amino acid sequence of SEQ ID NO:5, and nucleic acid sequences encoding same, to an unknown extent as permitted by the claims,

b) the specification lacks working examples wherein the leucine aminopeptidase amino acid sequence of SEQ ID NO:5, and nucleic acid sequences encoding same, are altered to any extent whatsoever,

c) in view of the prior art publications of record herein, the state of the art and level of skill in the art do not support such alteration, and,

d) unpredictability exists in the art where no members of the class of fungal aminopeptidases represented by the amino acid sequence of SEQ ID NO:5, has been altered by even a few amino acid sequence modifications.

Thus the scope of subject matters embraced by the phrase, "one or more amino acid(s) are substituted, deleted, inserted, added, or inverted" is unsupported by the present specification even if taken in combination with teachings available in the prior art.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-3 and 5-9 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 2, and 5-8 are indefinite because clauses (B) and (D) of both of claims 1 and 2 erroneously indicate that the elected aminopeptidase amino acid sequence is set forth in SEQ ID NO:4. But SEQ ID NO:4 is not an amino acid sequence. It is a nucleic acid sequence. The proper term for describing the elected, encoded, amino acid

sequence wherein the sequence of amino acids from position 1 through positions 519 is set forth is SEQ ID NO:5. Claims 5-8 are included in this rejection because they fail to resolve the ambiguity of claim 2 from which they depend.

Claims 1, 2, and 5-8 are indefinite in view of the recitations of "represented by" in clause (B) of claims 1 and 2 pertaining to the elected invention. The nature of such representation is not defined in the specification and no specific limitation of the extent of representation can be established on the basis of the disclosure, thus the artisan and the public seeking to determine the metes and bounds of the intended subject matter cannot know what is embraced by the claims. Amending clauses (B) of claims 1 and 2 to delete the term "represented by" and replace it with a standard transitional term, such as "comprising", will overcome this aspect of the rejection. Claims 3 and 5-8 are included in this rejection because they fail to resolve the ambiguity of claim 2 from which they depend.

Claims 1, 2 and 5-8 are independently indefinite in view of the recitations of "added or inverted" in clause (D) of both of claims 1 and 2 pertaining to the elected invention because these terms are redundant to, and duplicative of, the previously-recited terms "substituted" and "inserted". The artisan and the public seeking to determine the metes and bounds of the intended subject matter cannot know what distinguishes an "inserted" amino acid from an "added" amino acid, or know what distinguishes a set of "inverted" amino acids from a set of "substituted" amino acids, rendering the claims ambiguous. Amending clauses (D) of claims 1 and 2 to delete the superfluous terms "added" and "inverted" will overcome this aspect of the rejection. Claims 3 and 5-8 are included in this rejection because they fail to resolve the ambiguity of claim 2 from which they depend.

Claim 3 is independently indefinite due to the recitation, "under stringent conditions", in clause (D) of the claim pertaining to the elected invention because "stringent" is a relative term, without any dimension, and any particular set of hybridization conditions will always be "stringent" with respect to some other set of hybridization conditions. The artisan and the public seeking to determine the metes and bounds of the subject matter cannot know what extent of stringency is required to define an intended nucleic acid sequence, rendering the claims ambiguous. It is noted that page 7, lines 5 and 6 state two, particular, wash conditions that can be employed in DNA-DNA hybridization and that amending claim 3 to recite one of these conditions will establish specific conditions of stringency that would overcome this aspect of the rejection. Claim 9 further indefinite due to the recitation of "22, 33 kD" in clause (7) of the claim where the absence of a conjunction may be construed to indicate "and" or "both", making the claim ambiguous because the two masses are mutually exclusive. Amending the claim to replace the comma with the conjunction "or" will overcome this aspect of the rejection.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3 and 5 are rejected under 35 U.S.C. § 102(b) as being anticipated by Chang et al., 1989, made of record with Applicant's Information Disclosure Statement.

Chang et al. disclose the 510-amino acid sequence of the precursor form of the *Saccharomyces cerevisiae* vacuolar leucine aminopeptidase which shares 42% identity, 205 of 510, with the elected SEQ ID NO:5 herein, comprising many relative amino acid substitutions, additions, and deletions of SEQ ID NO:5 herein, thus meeting structural and functional limitations of claim 1. The nucleic acid sequence that Chang et al.

disclose to encode the *S. cerevisiae* aminopeptidase shares 42.4% identity with the nucleic acid sequence of SEQ ID NO:4 herein from position 199 through position 1599, inclusive, and will hybridize to SEQ ID NO:4 herein under some conditions more stringent than others, meeting limitation of claims 2 and 3. See Figure 3 of Chang et al. at page 6980. Chang et al. disclose the insertion of a nucleic acid sequence comprising the coding region of the *S. cerevisiae* aminopeptidase gene in a recombinant expression vector and the transformation of an *E. coli* host cell in order to conduct DNA sequence analysis, meeting limitations of claim 5. See page 6982.

Claims 1-3 and 5-8 are rejected under 35 U.S.C. § 102(b) as being anticipated by Smith et al., EP 0 359 164, made of record with Applicant's Information Disclosure Statement.

The co-inventors of Smith et al. are identical to the authorship of Chang et al., 1989, and Smith et al. identically disclose the 510-amino acid sequence of the precursor form of the *Saccharomyces cerevisiae* vacuolar leucine aminopeptidase that shares 42% identity, 205 amino acids in common, with the elected SEQ ID NO:5 herein and comprises many relative amino acid substitutions, additions, and deletions of SEQ ID NO:5 herein, meeting structural and functional limitations of claim 1. The nucleic acid sequence encoding the *S. cerevisiae* aminopeptidase of Smith et al. shares 42.4% identity with the nucleic acid sequence of SEQ ID NO:4 herein from position 199 through position 1599, inclusive, and will hybridize to SEQ ID NO:4 herein under some conditions more stringent than others, meeting limitation of claims 2 and 3 herein. See Figure 3 of Smith et al. Smith et al. disclose the insertion of a nucleic acid sequence comprising a region encoding the *S. cerevisiae* aminopeptidase in a recombinant expression vector in a context suitable for expression of the encoded aminopeptidase, the transformation of yeast, fungal and *E. coli* host cells with the expression vector, and a method for the recombinant production of the encoded aminopeptidase utilizing the

transformed host cell cultured in conditions conducive to such expression, meeting limitations of claims 5-8. See pages 13-15 of Smith et al.

Conclusion

Claims 4 and 9 would be allowable if amended to describe, respectively, an isolated nucleic acid molecule and an aminopeptidase isolated from *Aspergillus nidulans*, and if claim 4 were rewritten in independent form. Amending claims 1-3 to overcome the rejections stated above under 35 U.S.C. § 112, first and second paragraphs, would also overcome the rejection of claims above over the prior art. Deleting clauses of claims 1-4 pertaining to non-elected subject matter would then present a set of allowable claims.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to William W. Moore whose telephone number is 571.272.0933 and whose FAX number is 571.273.0933. The examiner can normally be reached Monday through Friday between 9:00AM and 5:30PM EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's Supervisory Primary Examiner, Dr. Kathleen Kerr, can be reached at 571.272.0931. The official FAX number for all communications for the organization where this application or proceeding is assigned is 571.273.8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571.272.1600.

William W. Moore
21 September 2005

NASHAAT T. NASHED, Ph.D
PRIMARY EXAMINER